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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/421,422 | 10/19/1999 | PEHR B. HARBURY | 8600-0197.30 | 4130 |

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PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

| EXAMINER |
|---|
| FRIEND, TOMAS H F |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1639 | |

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/421,422 | HARBURY ET AL. | |
| | Examiner | Art Unit | |
| | Tomas Friend | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

# Detailed Action

## Change of Art Unit Designation

**Please note:** The Art Unit location of this application in the PTO has changed from Art Unit 1627 to Art Unit 1639. To aid in matching papers to this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**.

## Status of the Application

A response to an office action was received on 17 October 2002 (Paper No. 13).

## Status of the Claims

Claims 1-14 were pending in the present application. Claims 11-14 were withdrawn from further consideration by the examiner in Paper No. 8. Claims 1-10 are examined on their merits.

## Withdrawn Rejections

The rejection of claims 1-10 under 35 U.S.C. 101 and the associated rejection under 35 U.S.C. 112, first paragraph over lack of utility are withdrawn.

The rejection of claim 1 under 35 U.S.C. 112, second paragraph, over the term "*reagent-specific compound intermediate*" is withdrawn.

The rejection of claims 9 and 10 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, is withdrawn.

## Maintained Rejections

The statutory basis for each of the following rejections may be found in a prior office action.

**Maintained Rejections - 35 U.S.C. 112, first paragraph**

Claims 1-10 remain rejected under 35 U.S.C. 112, first paragraph (enablement).

Applicants argue that references cited in the specification provide enablement for the synthesis of particular types of libraries such as peptides, nucleic acids, and small molecules. Applicants state that they do not understand how synthetic methods involving oligonucleotides to direct synthesis could be more unpredictable than methods not involving oligonucleotide tag-directed synthesis.

Applicants' argument has been carefully considered but it is not persuasive. Applicants' claimed invention is a method of synthesizing a plurality of compounds. The compounds synthesized at structurally undefined "*reactions sites*" and undefined locations on the oligonucleotides. There are no limitations on the compounds to be synthesized. Applicants refer to references in the specification which describe the synthesis of specific compound libraries such as peptides or oligonucleotides. A reference enabling the synthesis of any small molecule is not provided. Applicants, however, are not claiming a methods of synthesizing any structurally defined group or groups of compounds. Applicants' method, to be practiced commensurate with the scope of the claimed invention, requires that compounds be synthesized on an oligonucleotide template.

As stated in the office action, the predictability in the art for synthesizing any compound on "*reactions sites*" of oligonucleotides was low because one would have to experiment to determine annealing conditions that would simultaneously allow specific hybridization for many diverse sequences with diverse melting temperatures and to develop synthetic chemistry methods so that the oligonucleotide tag is not degraded and does not interfere with synthesis [i.e. the reactions involving the reagents], for example. The reaction conditions required for any given reagent depend on the reagent, what is reacting with the reagent, and the products being synthesized. This is how synthetic methods involving oligonucleotides to direct synthesis are more unpredictable than methods not involving oligonucleotide tag-directed synthesis. If no oligonucleotide tag is present, there are no issues of chemical or physical incompatibilities between the tag and the synthetic chemistry being performed.

**Maintained Rejections - 35 U.S.C. 112, second paragraph**

5. Claims 1-5 and 8-10 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the term "*nucleic acid tags*" does not provide one of ordinary skill in the art a means of determining the metes and bounds of the claimed method. It is not clear if the term encompasses "*oligonucleotide analogs*" as defined in the specification.

Applicants argue that the definiteness of claim language is measured solely on the elements recited in the claim and not in view of additional unrecited features described in the specification. Applicants did not indicate whether oligonucleotide analogs are encompassed by the term "*nucleic acid tags.*"

Applicants' argument has been fully considered but it is not persuasive. Applicants define "*nucleic acid tag*" on page 9 of the specification. Based upon that definition, it is not clear if nucleic acids have the same scope as or a different scope from "*oligonucleotide*" as defined on page 8 of the specification. One skilled in the art would normally consider an oligonucleotide as a nucleic acid of a limited length. Nucleic acid and oligonucleotide have different, open-ended, and partially functional definitions in the present specification, which cause confusion with regard to the metes and bounds of the term "*nucleic acid tags.*" In particular, it is not clear if the term encompasses "*oligonucleotide analogs*" as defined in the specification.

In claims 1 and 9, the term "*chemical reaction site,*" as defined in the specification, does not provide one of ordinary skill in the art a means of determining the metes and bounds of the claimed invention. Page 9 of the specification defines "*chemical reaction site*" as "*a chemical component capable of forming a variety of chemical bonds including, but not limited to...*" This definition provides no means for determining the metes and bounds of the claimed invention because any "*component*" of any compound is "*capable of forming a variety of chemical bonds.*"

Consequently, one of ordinary skill in the art would not have any structural or functional definition to distinguish what molecules are encompassed by the claim.

Applicants argue that the rejection is based upon the breadth of the term and draws an analogy to a court case involving a method of making a compound with a specific structure.

Applicants' argument has been fully considered but it is not persuasive. Applicants' claimed invention is not drawn to a method of making any specified compound or structure. The rejection is not based upon the scope of the term but the lack of any way to determine whether a specific functional group on a molecule is a "*chemical reaction site*" or whether any nucleic acid comprises a "*chemical reaction site.*" If the rejected term is interpreted as broadly as possible, any molecule would inherently possess a "*chemical reaction site.*" Alternatively, one skilled in the art could reasonable interpret the term to exclude functional groups normally found on nucleic acids. One skilled in the art would have to be able to determine the metes and bounds of "*chemical reaction site*" in order to avoid infringement.

In claim 1, it is not clear if each of the nucleic acid tags are reacted with the same reagent or if each tag is reacted with the same reagent, or if the same reagent may be used with more than one tag. Clarification is requested.

Applicants request clarification of the rejection but do not attempt to clarify or explain whether all tags react with the same reagent or if different tags are reacted with different reagents. It is not clear if only one (i.e. the same) reagent is reacted with all of the tags within a subset or if more than one reagent may be reacted with the tags within a subset, as long as each tag reacts with only one reagent.

In claim 2, the term "*oligonucleotide analog*" does not provide a means for determining the metes and bounds of the claim. The term is defined on page 8 of the specification as "*a nucleic acid that has been modified and which is capable of some or all of the biological activities of the oligonucleotide form which it was derived.*" One of ordinary skill would have no way of knowing what degrees of modification are encompassed by the term or what "*biological activities*" are encompassed. Base-pairing, for example can be reasonably be considered a physical property rather than a biological property.

Applicants argue that the examiner has misread and misquoted the definition of "*oligonucleotide analog*" (presumably because the words "chemical or" were inadvertently omitted from the quotation). The rejection, however, makes no mention of a chemical activity and is clearly based upon "*knowing what degrees of modification are encompassed by the term.*" Applicants have not addressed the issue of how one skilled in the art would know what degrees of modification are encompassed by the term.

In claim 3, it is not clear what the method is making. The preamble recites "*for use in forming a plurality of oligomers with different subunit sequences.*" Page 9 of the specification defines "*subunit oligomers*" as typically having 3 to 20 residue positions "*at which the subunit assumes one of a plurality of possible forms, e.g. different nucleic acid or amino acid side chains.*" Consequently, it is clear that nucleic acids and peptides are encompassed by the claim, but is not possible to determine what other types of molecules are included or excluded form the scope of the claim. Also, it is not clear what the metes and bounds of "*subunit*" are.

Applicants argue that the rejection is improperly based upon the breadth of the term, rather than the metes and bounds. Applicants' argument has been carefully considered but it is not persuasive. The rejection makes no mention of the breadth of the "*subunit oligomers*" but specifically states that it is not possible to determine the metes and bounds of what is encompassed by the term.

In claim 4, the term "*small molecules*" is not clear because the metes and bounds of the claim cannot be determined. It is not clear what molecular weight or molecular volume are to be used to differentiate between molecules that are small and those that are not.

Applicants argue that the rejection is improperly based upon the breadth of the term, rather than the metes and bounds. Applicants have not provided any argument regarding how the metes and bounds of "*small molecules*" are to be determined. The rejection makes no mention of the breadth of the term and cites specifically why the metes and bounds are not clearly defined.

In claim 4, the terms "*small molecules with different chemical sequences*" is not clear. The definition on page 9 of the specification provides no structural or functional standards that

can be used to determine the metes and bounds of the claim. The definition states that they are "*usually non-oligomeric*" so the term "*chemical sequence*" is difficult to interpret. In the art, "*sequence*" is associated with an oligomeric molecule and not with non-oligomeric molecules. It is not possible to interpret the meaning of "*sequence*" for non-oligomeric (non-linear) molecules.

Applicants assert that the definition of the term "*chemical sequences*" is properly defined in the specification. The rejection is not based solely upon the definition of "*chemical sequence.*" Applicants have provided no arguments addressing the basis of the rejection (i.e. apparent contradiction of non-oligomeric molecules having a sequence).

Claims 1 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: relationships between the sequences in the nucleic acid tags and the reactions that result in the directed synthesis of a plurality of compounds. It is not clear what relationships are required and responsible for the synthesis of different molecules onto the different tags or how the different reactions taking place on different tags are cooperatively related to the sequences present on the tags.

Applicants have asserted that figure 1 provides a visual representation, which may be used to clarify the relationships of the recited claim elements. Applicants' argument has been fully considered but it is not persuasive. Figure 1 represents one possible arrangement of the recited claim elements but the rejected claims are not limited to the configuration illustrated in figure 1. While the claims may be read in light of the specification, limitations may not be read from the specification into the claims.

In claim 8, it is not clear if the subpopulation nucleic acid tags to be used to carry out the method of claim 1 still have synthesized compounds attached or what method steps might be used to "*yield a subpopulation of nucleic acid tags.*" Presumably, the tags yielded in claim 8 cannot be used in the method of claim 1 if they are still attached to the compounds synthesized on them, but the claim does not recite method steps for removal of the tags from the synthesized

compounds. If the compounds are not removed from the tags, it is not clear how the method of claim 1 can be performed using the tags.

Applicants argue that the examiner has not provided reasoning as to why the compounds must be removed from the tags and has therefore failed to establish a prima facie case of indefiniteness. Applicants' argument has been carefully considered but it is not persuasive. The rejection is over the question as to whether or not the subpopulation nucleic acid tags to be used to carry out the method of claim 1 still have synthesized compounds attached or what method steps might be used to "*yield a subpopulation of nucleic acid tags.*" The examiner explicitly states that it is not clear whether the compounds must be removed from the tags. Consequently, no reasoning is provided for why the compounds must be removed from the tags. The examiner has stated that there are two possibilities: [1] the compounds are removed and [2] the compounds are not removed. It is not clear which is the case in claim 8 because it is not clear how identifying compounds can yield a subpopulation of nucleic acid tags unless they were chemically joined at some point.

Claims 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: method steps that provide a means for "*adding a chemical reaction site.*"

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Tomas Friend** at telephone number **(703) 308-4548**. The examiner's normal schedule is four, ten-hour days per week including Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Tomas Friend, Ph.D.
09 January 2002

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600